

Medical Professional Monograph

Cerebrolysin



Sequence - Combination of peptides which include:

BDNF, NGF, Enkephalin, Orexin, CNGF, P21

Molecular Composition:

25% low molecular weight peptides

75% free amino acids(Asp, Glu, Ser, His, Gly, Thr, Ala, Arg, Val, Met, Trp, Ile, Phe, Leu, Lys, Pro)



Indication and Usage Summary

- Alzheimer's Treatment
- Vascular Dementia Treatment
- Stroke Recovery
- Traumatic Brain Injury Recovery
- Peripheral Neuropathy
- MS
- Parkinson's

Description/Classification:

Cerebrolysin is a low molecular weight, porcine-derived peptide preparation with free amino acids that has a variety of clinical applications due its neuroprotective and neurotrophic properties. The preparation includes active peptide fragments include nerve growth factor, BDNF, Ciliary Nerve Growth Factor, P-21, enkephalins and orexin. Cerebrolysin has pharmacodynamic neurotrophic and neuroprotective activity that mimics endogenous neurotrophic factors. Neurotrophic factors are molecules that are responsible for growing, maintaining and repairing of neurons. They also have neuroprotective properties which strengthen neural pathways and the integrity of the neurons themselves. They are also responsible for promoting synaptic plasticity, which is a way the brain strengthens certain neural pathways. In situations where the brain needs to utilize neurotrophic factors to repair damaged neurons, such as in the case of neurological disease, Cerebrolysin can be administered to act as an analogue to endogenous neurotrophic factors. Studies have shown that the use of Cerebrolysin as treatment of neurodegenerative disease has often proved effective as a means of symptomatic treatment as well as pathological suppression in both the short and long term. Additionally, due to its neuroprotective properties, Cerebrolysin has been shown to have preventative potential for individuals who have genetic predisposition to developing Alzheimer's disease. While Cerebrolysin is not FDA approved in the United States, it is approved in many European and Asian countries for stroke, dementia and traumatic brain injury.



Mechanism of Action

Despite its wide range of application, the exact mechanism in which Cerebrolysin uses to promote neurogenic and neuroprotective activity is not completely known. The peptides of Cerebrolysin may interact with receptors of inhibitory modulators in the brain, including adenosine A1 and GABA_B. Cerebrolysin appears to have immunomodulatory effects that may attenuate inflammatory mechanisms associated with neurodegenerative disease. Studies have shown that Cerebrolysin reduces microglial expression and lipopolysaccharide (LPS)-induced interleukin-1 β release. The low molecular weight of the peptide preparation allows it to easily cross the blood-brain barrier, which makes intravenous injection the best method of administration to achieve pharmacologically significant levels of blood concentration. A study using rats was performed to examine entrance of Cerebrolysin components in to CNS tissue and found that mean tissue concentrations of Cerebrolysin across various regions of the brain were 170-237 ng per gram of tissue. When used to treat symptoms of Alzheimer's disease, Cerebrolysin has the effect of reducing phosphorylation of amyloid precursor protein (APP) and the amyloid-beta peptide by modulation of kinase proteins. The effect on APP suggests that Cerebrolysin's therapeutic effect on Alzheimer's is associated with management of APP's proteolytic product amyloid- β peptide. Additionally, Cerebrolysin mimics the effect of nerve growth factors (NGF) and therefore displays similar activity on dorsal root ganglia. NGF plays an important role in the survival of cholinergic neurons. Consequently, it is suggested that Cerebrolysin's ability to mimic NGF can help stabilize and prevent further development of AD via its neuroprotective effect on cholinergic neurons.¹ It was also found that Cerebrolysin increased the expression of the blood-brain barrier GLUT1 glucose transporter in the brains of young and old rats and *in vitro* via messenger RNA stabilization. This mechanism suggests the cognitive improvements associated with Cerebrolysin may be a result of increased glucose transport to the brain via the GLUT1 transporter.²

¹ Alvarez; et al. A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease. *European Journal of Neurobiology* 2008; 13: 43-54

² Boado, R; Brain-derived peptides increase the expression of a blood-brain barrier GLUT1 glucose transporter reporter gene. *Neuroscience Letters*, Dec 1996, Vol. 220(1), 53-56.



Dosage

1ml (215mg/ml) Daily injected subcutaneously

5mls (215mg/ml) combined with 250ml of IV liquid and dripped over 15 minutes.

Clinical Indications

Alzheimer's

Multiple studies have shown the ability of Cerebrolysin to improve symptoms of dementia due to Alzheimer's disease (AD) and vascular dementia (VD). Cerebrolysin mimics the activity of endogenous neurotrophic factors which have the ability to interact with mechanisms responsible for AD pathology. A study showed after a 4-week trial of intravenously administered Cerebrolysin on patients with mild to moderate AD, there was a significant improvement in the Alzheimer's Diseases Assessment Scale-cognitive subscale (ADAS-cog) relative to patients in the placebo group.³ A study has also shown the potential for Cerebrolysin to delay future progression of AD. In a 5-month follow-up examination of a study in which Cerebrolysin was intravenously administered 5 days per week over 4 weeks, 75% patients receiving Cerebrolysin showed improvement or no deterioration of AD symptoms, which is a significantly better result than patients in the placebo group. A separate study showed that after 6 months of Cerebrolysin treatment improved patients' Clinical Global Impression (CGI), which is a global measure of patient well being, relative to placebo. Patients with a copy of the Alzheimer's-linked APOE4 allele may benefit from Cerebrolysin as a preventative measure for development of dementia symptoms. A study in which mice were bred to be homozygous APOE4, tested the effect of Cerebrolysin treatment on cognitive function by having the mice navigate a Morris water maze. APOE4 homozygous mice treated with Cerebrolysin displayed significant improved performance in the maze relative to APOE4 homozygous mice treated with saline.

³ Allegri, R.F.; Guekht, A.. Cerebrolysin improves symptoms and delays progression in patients with alzheimer's disease and vascular dementia. *Drugs of Today* 2012, 48 (Supplement A): 25-41. DOI: 10.1358/dot.2012.48(Suppl.A).1739721



Vascular Dementia

Cerebrolysin has been shown to improve symptoms caused by vascular dementia (VD). A study was performed in which patients diagnosed with VD were given either 20 mL intravenous infusion of Cerebrolysin once daily 5 days per weeks over 4 weeks or a placebo. The results showed that VD patients treated with Cerebrolysin displayed significantly greater improvement in ADAS-cog scores as well as CIBIC+ scores relative to patients who received a placebo.⁴ The primary clinical treatments for VD are antiplatelet and hemorheologic drugs which primarily symptomatic treatments. The exciting aspect of using Cerebrolysin as a treatment is its mechanism of action that works along the pathological cascade. This means that Cerebrolysin has potential to not only treat symptoms, but also address the underlying neurological cause and help slow the diseases progression.

Parkinson's Disease

Studies have shown the Cerebrolysin may have clinical applications in treatment of Parkinson's Disease (PD). One such study, which looks into treatment of PD linked to traumatic brain injury (TBI), administered Cerebrolysin to mice that had been experimentally given PD symptoms and subjected to head trauma. The results indicated that nanowired Cerebrolysin along with mesenchymal stem cells provided neuroprotective benefits to mice with PD that were subjected to TBI.

Studies have suggested that PD in humans can be linked to increased levels of alpha-synuclein (ASNC) and oxidative stress in the brain. A study was performed in which PD was experimentally induced in mice and their levels of ASNC and nitric oxide synthase (nNOS) were measured. ASNC and nNOS levels were found to be elevated. Treatment of the mice with Cerebrolysin resulted in a reduction of ASCN and nNOS expression. This result displays potential in Cerebrolysin's ability to treat Parkinson's linked to increased ASNC and oxidative stress.⁵

⁴ Allegri, R.F.; Guekht, A.. Cerebrolysin improves symptoms and delays progression in patients with alzheimer's disease and vascular dementia. *Drugs of Today* 2012, 48 (Supplement A): 25-41. DOI: 10.1358/dot.2012.48(Suppl.A).1739721

⁵ Sharma, A; et al. Nanodelivery of cerebrolysin induces neuroprotection in Parkinson's disease. *Neurochem Neuropharm* 2017, 3:2(Suppl). DOI: 10.4172/2469-9780-C1-005



Acute Stroke Recovery

The use of Cerebrolysin as an aid in motor recovery after acute ischemic stroke onset has been shown to be beneficial in conjunction with standard rehabilitation. Cerebrolysin has been shown to have neurogenic properties, which may be relevant in accelerating neural restoration after a stroke occurs. A study which administered a 21-day Cerebrolysin treatment complementary to a standard rehabilitation program for patients with moderate to severe stroke-induced motor function impairment showed a significant improvement in motor function for patients with severe impairment.

Studies have also explored the use of Cerebrolysin in patients who have suffered hemorrhagic stroke. Patients were initially screened within 24 hours from the onset of stroke and given 50 mL cerebrolysin via intravenous infusion once daily for 10 days. The results showed statistically insignificant results between the Cerebrolysin group and placebo group. However, it was concluded that administration of Cerebrolysin to hemorrhagic stroke patients was safe and well tolerated and that future studies should be performed with larger sample sizes to further explore Cerebrolysin's implications on hemorrhagic stroke recovery.⁶ Another study which also linked Cerebrolysin's neurogenic properties to ischemic stroke recovery found significant positive results using the NIH Stroke Scale, the modified Rankin Scale and the Clinical Global Impression as metrics.

Peripheral Neuropathy

Due to Cerebrolysin's neurogenic properties, its application as a treatment for peripheral neuropathy has been hypothesized. One study, which specifically looked at diabetic peripheral neuropathy, was performed in which mice were given a diet that resulted in type-2 diabetes. These diabetic mice were treated with Cerebrolysin for 10 days. After treatment, it was found that the number, diameter and area of the diabetic mice's' myelinated nerve fibers increased in the sciatic nerve. The mice were also subject to a series of tests that indicated presence and severity of peripheral neuropathy. The mice treated with Cerebrolysin outperformed the untreated mice in all measures. These results indicate Cerebrolysin could be a powerful treatment to counter the effects of diabetic peripheral neuropathy. A separate study found that

⁶ Heiss, W. et al. Cerebrolysin in Patients With Acute Ischemic Stroke in Asia Results of a Double-Blind, Placebo-Controlled Randomized Trial. *Stroke Journal of the American Heart Association*. 2012;43:630-636; originally published online January 26, 2012



administration of Cerebrolysin in rats significantly increased the number of myelinated axons as well as the thickness and diameter of the myelin sheaths.⁷ This finding illuminates potential use for Cerebrolysin as treatment for MS.

It also has some effects on pain and neuropathy in non-diabetic pathologies. A study was performed that shows a potential application for treatment of mechanical allodynia. Mechanical allodynia was induced in the back paw of a sample of rats. The metric used was the speed at which the rat withdrew its paw after stimulation. The results indicated that the reduction in withdrawal time resulting from induce mechanical allodynia was significantly ameliorated after Cerebrolysin treatment. While more studies need to be performed, these results illuminate the potential for Cerebrolysin's application to treating pain caused by peripheral nerve disease.

Migraine

Research suggests that administration of Cerebrolysin may help reduce symptoms of chronic migraine. Symptoms of chronic migraine were induced in laboratory rats via injection of nitroglycerin (NTG) over the course of 10 days. A variety of behaviors were observed that indicate discomfort due to migraine symptoms. These behaviors included Mechanical and thermal withdrawal thresholds of the hind paw, head grooming behavior and light-aversive behavior. Rats treated with Cerebrolysin over the course of the migraine inducing NTG administration displayed markedly reduced mechanical and thermal hyperalgesia, head grooming, and light-aversive behaviors induced by NTG. In addition to migraine symptom behavior, blood concentrations of calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) were measured. Relative to rats not treated with Cerebrolysin, rats injected with Cerebrolysin showed significantly decreased blood levels of CGRP, PACAP, and pro-inflammatory cytokines (TNF- α and IL-1 β).⁸ These findings suggest the power Cerebrolysin may have to treat migraine symptoms and reduce concentration of markers in the blood related to chronic migraine.

⁷ Pavel et al. Ciliary neurotrophic factor promotes motor reinnervation of the musculocutaneous nerve in an experimental model of end-to-side neurotomy. *BMC Neuroscience*, 01 June 2011, Vol.12(1), p.58

⁸ Mahmoudi, Mohaddes, Erfani, Sadigh-Eteghad, Karimi, Rajabi, . . . Farajdokht. (2018). Cerebrolysin attenuates hyperalgesia, photophobia, and neuroinflammation in a nitroglycerin-induced migraine model in rats. *Brain Research Bulletin*, 140, 197-204.



Cerebrolysin Constituents:

Nerve Growth Factor: An important protein for development and maintenance of neurons, specifically neurons involved in pain, temperature and touch sensation. Nerve growth factor functions by binding to either the NTRK1 receptor or the p75NTR receptor which are both found on the surface of sensory neurons.

Brain-Derived Neurotrophic Factor (BDNF): Protein found in the brain and spinal cord that is responsible for growth, maturation and maintenance of neurons. In the brain, BDNF is active in the synapse and is important in regulating synaptic plasticity.

Ciliary Neurotrophic Factor (CNTF): A brain derived protein that promotes neuron survival and axonal outgrowth during neuronal development.

Enkephalins: Functions as a ligand for the kappa-type opioid receptor. Competes with and mimics effects of opiate drugs and therefore plays a role in pain perception and response to stress.

Orexin: Functions as a ligand which binds to orphan G-protein coupled receptors that play a role in regulation of sleep and arousal as well as feeding behavior, metabolism and homeostasis.

P21: The pentamer Ac-DGGLAG-NH₂ is a peptide fragment of Cerebrolysin that has been found to play a role in neurogenesis and neuronal plasticity.

Conclusions

The clinical applications of Cerebrolysin are profound and diverse. As a peptide preparation with neurotrophic and neuroprotective capabilities, Cerebrolysin's impact on combating the rising prevalence of neurodegenerative diseases is an exciting development in the medical field. Dementia due to Alzheimer's and vascular ischemia, Parkinson's disease, peripheral neuropathy, Multiple sclerosis, and traumatic brain injury are all diseases with devastating physiological consequences and Cerebrolysin may be key in their treatment and prevention.



Allegrì, R.F.; Guekht, A. "Cerebrolysin Improves Symptoms and Delays Progression in Patients With Alzheimer's Disease and Vascular Dementia." *Drugs of Today* 2012, 48 (supplement A), pp. 25-4., DOI: 10.1258/dot.2012.48(Suppt.A).1739721

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Mahmoudi, Mohaddes, Erfani, Sadigh-Eteghad, Karimi, Rajabi, . . . Farajdokht. (2018). Cerebrolysin attenuates hyperalgesia, photophobia, and neuroinflammation in a nitroglycerin-induced migraine model in rats. *Brain Research Bulletin*, 140, 197-204.

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vii. Gauthier, S., Proaño, J., Jia, J., Froelich, L., Vester, J., & Doppler, E. (2015). Cerebrolysin in Mild-to-Moderate Alzheimer's Disease: A Meta-Analysis of Randomized Controlled Clinical Trials. *Dementia and Geriatric Cognitive Disorders*, 39(5-6), 332-347.